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Insulin-induced skin lipohypertrophies: A neglected cause of hypoglycemia in dialysed individuals with diabetes

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ABSTRACT

Background: Diabetes mellitus (DM) is the leading cause of end-stage renal disease and 50% of dialysis patients are insulin-treated.
Aim: to search for unexplained hypoglycemia (HYPO).
Methods: identify a possible cause of HYPO due to altered insulin absorption.
Results: insulin injected into subcutaneous lipo-hypertrophy (LH) nodules leads to unpredictable HYPOS.
Conclusion: looking for LH systematically and training patients to the best injection technique are new challenges for nephrologists to reduce HYPO and emergency hospitalization rates, thus sparing healthcare resources and improving the quality of life of insulin-treated dialysis patients.

The incidence and prevalence of type 2 diabetes mellitus (T2DM) have grown all over the world for the last ten years or so, thus causing a marked increase in the number of people developing diabetic kidney disease (DKD) [1].

Apropos of that, it is also important to note that chronic kidney disease (CKD) often occurs per se, so that patients may suffer CKD as an add-on to, rather than a complication of T2DM. Nevertheless, by accounting for approximately 50% of cases, DKD is one of the most frequent complications of T2DM, leading to end-stage renal disease (ESRD) in developed countries. Incidence rates for DKD-related ESRD remain stable over the past few years [2,3], with high-risk subgroups clearly identified as middle-aged African Americans, Native Americans, and Hispanics, likely due to the ever-increasing earlier-onset disease rates in these populations leading to longer and longer-duration DM complications [4].

Incidence rates for DKD-related ESRD remain stable over the past few years [2,3], with high-risk subgroups identified as middle-aged African Americans, Native Americans, and Hispanics, likely due to the ever-increasing earlier-onset disease rates these populations leading to longer and longer-duration DM complications [4]. The overall DKD-related health costs are extraordinarily high, mainly depending on the solid relationship linking DKD to cardiovascular disease (CVD) and ESRD [3]. For example, in 2011, overall expenditures for diabetes and CKD were approximately $25 billion in the Medicare population, mostly involving over65s, whose yearly costs per person were $20,000 at the transition to ESRD compared to the $40,000 calculated for patients <65 years of age. According to a positive and negative function, albuminuria and glomerular filtration rate (GFR) appear independently and additively associated, respectively, with all-cause and CVD mortality. The observation that most of the excess CVD prevalence in T2DM is accounted for by DKD strengthens this finding [5].

Hypoglycemic risk increases at estimated glomerular filtration rate (eGFR) levels <60 ml/min/1.7m2 (i.e., in the presence of CKD), partly due to decreased kidney-related gluconeogenesis and slower glucose-lowering drug clearance rate [6,7]. Therefore, many

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hypoglycemic agents require dose adjustments in people with DKD. Moreover, insulin clearance rate decreases parallel to eGFR [6–8], so that even more frequent self-monitoring of blood glucose (SMBG) than usual and accurate individualized dose titration are critical to achieving treatment goals while also avoiding hypoglycemia (Hypo) [6–8], which older individuals are per se at greater risk for [9,10]. Clinicians should also pay special attention to the fact that patients on long-term dialysis experience malnutrition, which, in turn, often asks for less exogenous insulin [6]. All the above explains why current guidelines suggest less stringent HbA1c treatment targets in older patients with DKD [11].

Due to the markedly reduced eGFR observed in renal failure, only a few DM-related medications are recommended in patients on dialysis, including insulin which, however, being burdened by a high Hypo risk, requires a substantial dose reduction over time [12–14]. Indeed, despite mostly asymptomatic, Hypos occur pretty often in dialyzed people as a result of factors different from glucose-lowering agents, including dietary errors, prolonged fasting, alcohol intake, chronic malnutrition, malignancies, heart/liver/kidney failure, adrenal or thyroid hormone deficiency, beta-blockers or other drugs.

Hypo risk increases in patients with advanced DKD transitioning to dialysis. The rate of severe Hypos requiring hospitalization further increases soon after that, by displaying a solid association with one-year mortality [15], mainly because, as well known to nephrologists, a marked intra- and between-day glycemic variability (GV) occurs, which further increases CVD risk resulting from intermittently enhanced insulin clearance rate [14,16–20]. In greater detail, Hypo risk progressively increases during the critical dialysis transition period, being more strongly associated with stroke, insulin utilization, and hemodialysis (rather than peritoneal dialysis) [15].

GV, i.e., the occurrence of several episodes of hyper- and hypoglycemia within a relatively short period, is a challenge for all insulin-treated patients, especially those with ESRD or on chronic hemodialysis. Besides focusing on insulin type and the amount needed to compensate glucose intake when reviewing their patients' glucose logs or meter downloads, clinicians should consider adherence to the appropriate insulin injection technique (IT) as, at least, equally relevant to attain optimal metabolic control.

Although being very well known due to carefully controlled studies led on healthy resting subjects, insulin pharmacokinetics (PK) is influenced by many factors, including whether the hormone gets into the subcutaneous (SC) fat or the muscle.

The SC route is used for insulin delivery because expected to ensure much more consistent hormonal absorption rates than intramuscular injections (IMIs). Nevertheless, being longer than needed, many needles commonly used with insulin pens and syringes increase the risk for IMIs, which may markedly and unpredictably increase insulin uptake, indeed, both per se and depending on whether the muscle is at rest or exercised [21]. Patients are often taught to lift skinfolds or at least to angle needles by 45° to the skin to minimize such risk. However, the best solution consists of simply promoting the utilization of short needles.

Moreover, improper IT entails an even more worrying consequence, i.e., skin lipohypertrophy (LH), which, indeed, LH affects several insulin-treated patients [22–26] (Figs. 1–3). Poor injection site rotation and frequent needle reuse are the most common factors associated with LH, as injecting into LH can reduce insulin absorption and expected activity, thus allowing postprandial glucose to increase sharply and causing highly variable insulin uptake [26]. Despite this, health care professionals (HCPs) do not perform injection site inspections routinely, hence the "unexplained" nature of many blood glucose fluctuations. Approximately half a billion people have diabetes [27]. Insulin users are estimated

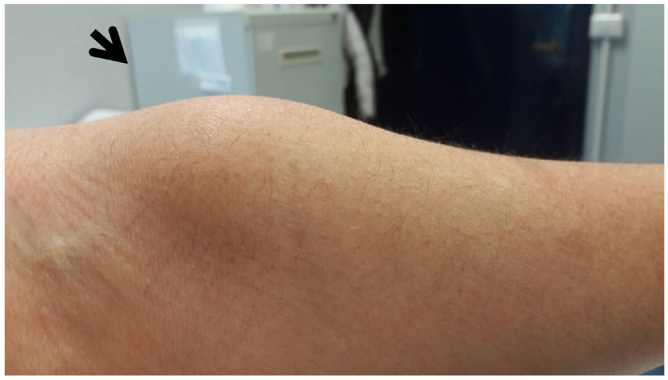

Fig. 1. Easily seen proximal forearm (an abnormal injection site) LH lesion.

to be 150–200 million worldwide [28], including all people with type 1 diabetes and around 20–25% of those with T2DM, primarily through repeated daily injections. Despite being the most effective glucose-lowering medication for diabetes, insulin has one of the lowest therapeutic indexes among medications and is endowed with a high Hypo risk, according to the Institute for Safe Medications Practices [29]. Improper IT can further increase such a risk.

LH is the most frequent local complication of both insulin injections [22–26,30] and pump-related infusions [31,32], with some 50% prevalence rates according to different studies from various countries [30]. As altered PK due to delayed or erratic absorption from LH adversely affects insulin action (i.e., pharmacodynamics, PD), and, therefore, glycemic control [33–36], HCPs taking care of insulin-treated patients should make it a habit to check for LH frequently (at least yearly), especially when facing high GV or unexplained Hypos.

A recent crossover glucose clamp study showed dramatic insulin PK and PD changes after injections into LH areas, with a 3- to 5-fold more significant variability than healthy skin. A controlled mixed-meal tolerance test in the same study showed prolonged hyperglycemia after injection into LH lesions, as well [26]. Also, patients with LH require significantly higher daily insulin doses than those without LH [22,24], which leads to substantially increased direct costs for patients or payers. When patients stop injecting insulin into LH lesions and start using healthy tissue, Hypo risk and GV, daily insulin requirement, and related costs consistently decrease [22,25,37]. The key message, in the end, is that insulin injections should never get into LH areas.

In a recent multicenter observational study focusing upon LH identification at injection sites in an extensive series of dialyzed diabetic subjects, for the first time to our knowledge, we found that over 50% of ESRD/dialyzed patients suffer LH due to inappropriate IT, including missing injection site rotation, long-needle utilization and too small skin areas chosen for injections [38]. The damage caused to hemodialyzed insulin-treated patients by LH-dependent increase in GV and Hypo prevalence rates is more relevant than expected from periodic dialysis on/off switch. Therefore, education to the appropriate IT would markedly decrease GV, Hypo risk, and diabetes costs in such a clinical set, too [22,23,25].

In conclusion, as great GV and frequent symptomatic/severe Hypos are independent risk factors for CV-related and all-cause mortality, as well as hospitalization [39–43], we firmly believe that future investigations concerning Hypo risk in patients on dialysis should always take into account the outstanding contribution to that risk provided by LH lesions. Moreover, all HCPs involved in dialysis units should be aware of best practices to prevent LH development and progression [44] to set patients free

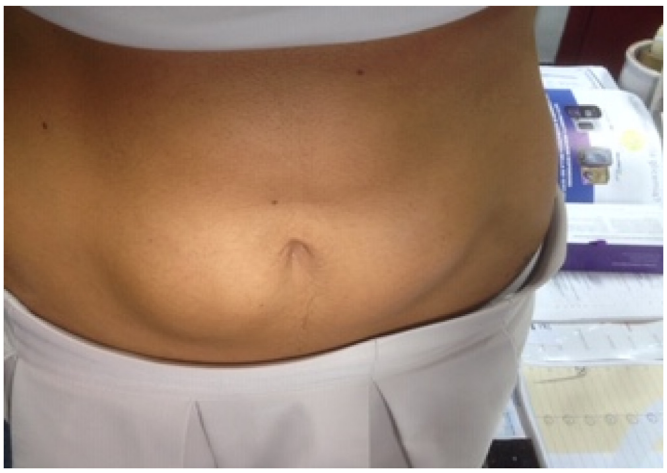

Fig. 2. Easily seen proximal forearm (an abnormal injection site) LH lesion.

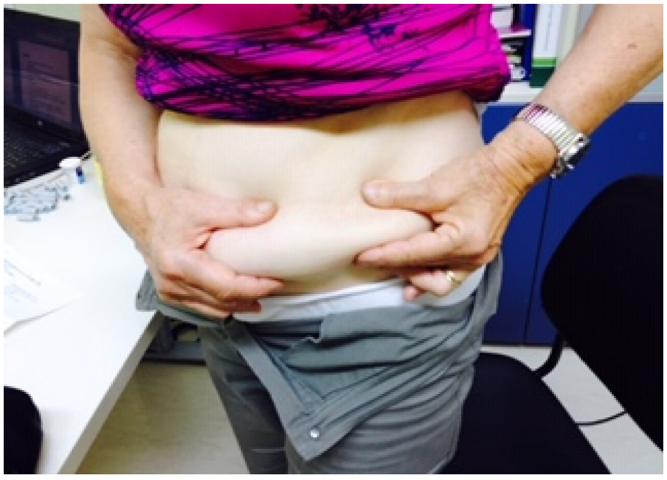

Fig. 3. Easily seen proximal forearm (an abnormal injection site) LH lesion.

from the associated metabolic burden bound to disrupt further their ESRD-related intrinsically poor quality of life.

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Authorship

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published: Sandro Gentile, Giuseppina Guarino, Teresa Della Corte, Ersilia Satta, Carmine Romano e Carmelo Alfarone, and Felice Strollo.

Authorship contributions

SG and FS created the paper and wrote it. GG, ES, TDC, CA, CR, critically read and approved the paper. All approved the final text. All Collaborators critically read and approved the final text.

Compliance with ethics guidelines

This study was conducted in conformance with good clinical practice standards. The study was led in accordance with the original Declaration of Helsinki and its later amendments, and was approved by Vanvitelli University, Naples, Italy. Written informed consent was obtained from all patients before publishing their photos.

Open access

Compliance with ethics guidelines

This article is based on previous conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Declaration of competing interest

None of the authors has conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2021.05.018.

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